| LETTER TO THE EXAMINER | | |
|---|---|---|
| | Application # | 10/629,858 |
| | Confirmation # | 6153 |
| | Filing Date | 30 July 2003 |
| | First Inventor | CARTER et al. |
| | Art Unit | 1625 |
| | Examiner | Dentz, Bernard I. |
| | Docket # | P07634US01/BAS |

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

S I R:

Further to Applicants' response to the Official Action filed April 13, 2005, enclosed is the executed Declaration under 37 C.F.R. § 1.132 for Dr. Daniel C. Carter, Ph.D.

Applicants submit that in light of the enclosed executed Declaration, and in light of the amendments and arguments in Applicants' response, the present case has been placed in condition for immediate allowance, and such action is earnestly solicited.

Respectfully submitted,
STITES & HARBISON PLLC

Date: April 25, 2005

B. Aaron Schulman
Registration No. 31,877

1199 North Fairfax Street, Suite 900
Alexandria, Virginia 22314
(703) 739-4900

1315LT:5944:14017:1:ALEXANDRIA

| DECLARATION UNDER 37 CFR § 1.132 OF DR, DANIEL C. CARTER, PH.D. | | |
|---|---|---|
| | Application # | 10/629,858 |
| | Confirmation # | 6153 |
| | Filing Date | 30 July 2003 |
| | First Inventor | CARTER et al. |
| | Art Unit | 1625 |
| | Examiner | Dentz, Bernard I. |
| | Docket # | P07634US01/BAS |

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

S I R:

I, Dr. Daniel C. Carter, Ph.D., declare as follows:

1. I am one of the inventors of the above-identified application, and I have also been the named inventor in numerous other patents in the general field of protein crystallography included several relating specifically to albumin. I am also the author of numerous articles in the field of protein crystallography including many articles relating to the binding properties and complexes formed with human serum albumin. I am thus well familiar with the field of the invention.

2. The present invention relates to the need to develop safer and more effective alternative medicines to Warfarin which has been on the market for over 50 years and used in the prevention of thrombotic diseases and stroke. One particular brand of warfarin is racemic sodium warfarin (also known as Coumadin), which is a product of Bristol Myers Squibb with current U.S. annual sales of approximately $230 million, and the preparation of this warfarin is well documented and would be readily known by those skilled in the art. However, despite the large annual sales, and despite the fact that it is estimated to prevent twenty strokes per induced bleeding episode,

warfarin is under-used because of the difficulty of controlling dosage and the fear of inducing bleeding. Coumadin's primary mode of action involves inhibiting microsomal vitamin K epoxide reductase and interfering with a number of vitamin K dependent blood clotting factors, including Factors II, VII, IX and X. Warfarin is thus a therapeutic with a low margin of safety and is considered 99% bound to plasma albumin *in vivo*, and it represents the precise reason for the development of the alternative compounds of the invention. The formula of Warfarin is as follows:

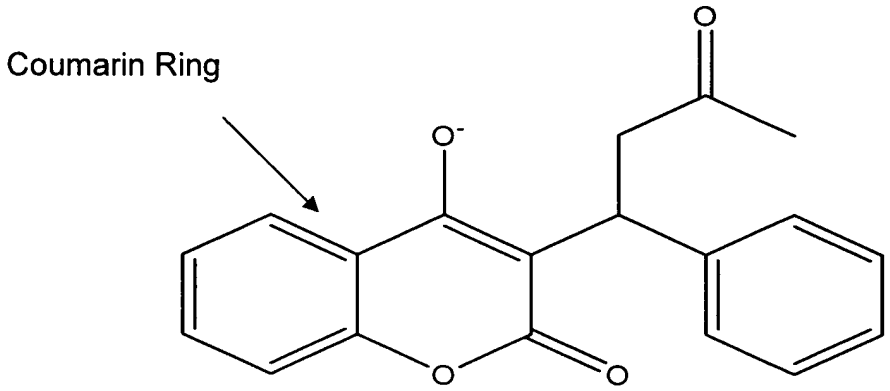


Figure 1 – Chemical structure of Warfarin

3. Our invention was to use my company's technology, including our high resolution CADEX™ advanced crystallographic techniques, to provide a closer picture of the structures of human serum albumin complexed with warfarin racemic mixtures and individual isomers, and to use this information to determine types of changes to warfarin that would have beneficial results in terms of improved binding properties. For example, changes that affect inhibition for vitamin K epoxide reductase should be avoided since it has been shown that only the coumarin ring is essential for the inhibition.

4. Therefore, the compounds of our invention have resulted from our discovery that substitutions at the phenol ring on the other end of the warfarin molecule (Figure 1) can favorably affect the pharmacokinetics and safety of this important drug. These modifications were also chosen because of the chemical availability of the coumarin ring (see Figure 1) which makes it easy for one skilled in the chemical arts to make the simple changes to the structure of warfarin to obtain the claimed compounds of the invention. Accordingly, relatively minor chemical synthesis starting with the known warfarin compound and utilizing standard and straightforward chemical reactions well known to those skilled in the art is all that is necessary to obtain the compounds of the invention. Indeed, this information has allowed my inventive group to readily synthesize compounds in accordance with this invention using ordinary skill in the chemical arts.

5 In light of the fact that the compounds of the invention represent specific chemical changes well known to those of ordinary skill in the art at specific locations in a compound (warfarin) that is well known and easily synthesized, it is clear that the presently claimed compounds can be readily be obtained by one of ordinary skill in the art, and that the Examiner's objection on the basis that one skilled in the art would not be able to make and use this invention is not correct.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

4/22/05
Date :

Dr. Daniel C. Carter, Ph.D.

1315LT:5944:13475:1:ALEXANDRIA